

## PATENT ABSTRACTS OF JAPAN

(11)Publication number : 08-169849

(43)Date of publication of application : 02.07.1996

(51)Int.Cl.

A61K 49/04

(21)Application number : 03-349293

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(22)Date of filing : 30.10.1991

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(54) BARIUM SULFATE CONTRAST MEDIUM FOR USE IN CT

(57)Abstract:

PURPOSE: To obtain the subject low-viscosity contrast medium consisting mainly of barium sulfate, excellent in redispersibility even after precipitated.

CONSTITUTION: This contrast medium is obtained by incorporating a barium sulfate suspension with a swellable additive such as an insoluble disintegrant (a physiologically permissible and water-insoluble high-molecular compound, e.g. carboxymethylcellulose). It is appropriate that the barium sulfate concentration of the suspension be 0.5-6.0wt.% and the particle diameter thereof 0.5-2 $\mu$ m. The water-insoluble high-molecular compound accounts for 0.2-3wt.% of the suspension. The contrast medium also contains a conventional antiseptic, dissolution auxiliary, defoaming agent, sweetener, flavor, perfume, etc., according as appropriate. When the contrast medium is homogeneously agitated and then allowed to stand, the barium sulfate and additive freely or flocculatingly precipitate, thus resulting in mixed precipitation at the bottom of a vessel or forming a sediment layer (soft cake) of the barium sulfate in a layer on the additive.

Therefore, even after being left to stand for a long time, this contrast medium exhibits excellent redispersibility merely by simple handy shaking when to be used.

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## CLAIMS

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[Claim(s)]

[Claim 1]An X-ray contrast medium for CT there being barium sulfate and physiological admission nature, and containing an insoluble high molecular compound.

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## DETAILED DESCRIPTION

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[Detailed Description of the Invention]

[Industrial Application]This invention is the low viscosity which uses barium sulfate as the main ingredients, and relates to the new X-ray contrast medium for TC which has the redispersibility which was excellent even if it sedimented.

[Description of the Prior Art]The X-ray contrast medium for alimentary canals which uses barium sulfate as base resin is mainly marketed and taken in the form of the mixture. Since specific gravity of barium sulfate is as high as about 4.5, in pharmaceutical-preparation-izing of the suspension which sedimented very easily and was stabilized, the kind of suspension stabilizer and selection of the amount used are very important for it. However, even if these selections are appropriate, in order not to avoid sedimentation of some barium sulfate but to urge re dispersion to it, 2 or 3 shake of a container will be temporally needed at the time of use. That is, the consideration for making redispersibility good also hits pharmaceutical preparation, and is an important matter. In CT diagnosis which has spread recently, a barium sulfate contrast medium is low concentration farther than the barium sulfate contrast medium (in the cases of many 30 to 150%) with which the barium sulfate concentration in pharmaceutical preparation is usually conventionally used for diagnosis of the stomach or intestines with 0.5 to 6.0 % of the weight. Thus, if low-concentration pharmaceutical preparation of redispersibility is not good, naturally the concentration of barium sulfate at the time of use will fall from predetermined concentration. The influence is farther [ than the high-concentration contrast medium with high barium sulfate concentration usually used for the stomach or intestines ] great. Therefore, in the case

of the contrast medium for CT, it is very important to build a suspensibility and the pharmaceutical preparation outstanding in respect of redispersibility. That is, if you make it the thing of different concentration for every patient prescribed for the patient, it will result in different contrast on the resulting image being acquired, and interfering with diagnosis. In order to aim at making change of concentration as small as possible, what is necessary will be just to be able to return to the state immediately after manufacture by shaking at the time of use. In order to manufacture this low concentration suspension for CT conventionally, a water soluble polymer and surface-active agents (for example, gelatin, gum arabic, sodium alginate, carboxymethylcellulose sodium, etc.) were used, but. One to two months after preparation, barium sulfate sediments, and the pharmaceutical preparation is condensed firmly, and has a fault which does not fully carry out re dispersion. The solution is desired.

[A technical problem and a means to solve] This invention has the physiological admission nature by which barium sulfate was not conventionally used for 0.5 to 6.0% of the weight of the water suspension agent, and an insoluble high molecular compound is made to contain. 0.5 or less % of the weight has [ the barium sulfate suspension for CT diagnosis / the contrast on a picture ] the insufficient water suspension concentration of barium sulfate in CT diagnosis, and a picture becomes indistinct. On the other hand, at 6 % of the weight or more, since there is a problem that the artifact that the high portion of contrast and a low portion run radiately on a picture arises, it is used in this density range. As barium sulfate, 0.5-2micro are suitable for particle diameter, and it is 10-1.5micro preferably. There is physiological admission nature and carboxymethyl cellulose, carboxymethyl calcium, starch alginic acid, calcium alginate, hydroxy propyl starch, etc. are mentioned as a high molecular compound of insoluble liquid. These compounds have the characteristic which it is insoluble, it swells in water and does not show viscosity in it. As the amount used, 0.2 to 3 % of the weight is especially good, and 1 % of the weight is suitable. In 3 % of the weight, in administration, it becomes a problem and redispersibility does not bear use bad at 0.2% or less. The butyl parahydroxybenzoate by which normal use

is furthermore carried out to the contrast medium in this invention, Solubilizing agents, such as antiseptics, such as ethyl p-hydroxybenzoate and dehydroacetic acid soda, and propylene glycol, It cannot be overemphasized that perfume, such as a defoaming agent like dimethylsiloxane, saccharin sodium, sweeteners like sugar, corrigent like citrate, ice-cream soda essence, and strawberry essence, may be suitably used together. The process of suspension should just follow the method currently performed conventionally, and a special method is not needed. [Example]Next, this invention is not restricted by these examples although the example of this invention is given.

A. Preparation example 1 barium sulfate (mean particle diameter of 1.0micro) of a contrast medium. 0.5 g -- sugar [ ] by carboxymethylcellulose sodium (die cell 1220) 3g Daicel Chemical Industries, Ltd. -- 0.5 g -- the sodium-dehydroacetate 0.06g above-mentioned ingredient -- the optimum dose of purified water -- homomixer yogurt essence 0.05g -- 3 glorification -- study (T. K.) It is made to distribute for 3 minutes by the usual method in HOMO MIXER and the product made from Special machine Industry. Next, added 3 g carboxymethyl cellulose (the product made from NICHIRIN, NS-300), purified water was made to distribute for 1 minute as 100 ml, and the barium sulfate contrast medium for CT was prepared. (A-1)

In example 2 Example 1, the barium sulfate contrast medium for CT was prepared like Example 1 except having used 1.5 g for barium sulfate. (A-2)

In example 3 Example 1, 2.5 g was used for barium sulfate (it is below the same). (A-3)

In example 4 Example 1, 3.5 g was used for barium sulfate (it is below the same). (A-4)

In example 5 Example 1, 4.5 g was used for barium sulfate (it is below the same). (A-5)

Let a sample be A series above.

example 6 barium sulfate [ ] -- 0.5 g -- the carboxymethylcellulose sodium (die cell 1220) 2g Daicel Chemical Industries, Ltd. make sodium-dehydroacetate 0.06g above-mentioned ingredient -- the optimum dose of purified water -- a homomixer (T.) [ K HOMO MIXER and ] It is made to distribute for 3 minutes by the usual method in the product made from Special machine Industry. Next, added 3 g carboxymethyl-cellulose calcium (the product made from NICHIRIN, ECG505), purified water was made to distribute

for 1 minute as 100 ml, and the barium sulfate contrast medium for CT was prepared. (B-1)

In example 7 Example 6, 1.5 g was used for barium sulfate (it is below the same). (B-2)

In example 8 Example 6, 2.5 g was used for barium sulfate (it is below the same). (B-3)

In example 9 Example 6, 3.5 g was used for barium sulfate (it is below the same). (B-4)

In example 10 Example 6, 4.5 g was used for barium sulfate (it is below the same). (B-5) Let a sample be B series above.

0.5 g comparative example 1 barium sulfate (the same thing as Example 1) -- carboxymethylcellulose sodium (die cell 1220) 3g Daicel Chemical Industries, Ltd. make yogurt essence 0.05g -- 3 glorification -- study The sugar 0.5g above-mentioned ingredient. It is made to distribute for 3 minutes by the usual method in purified water optimum dose at a homomixer (T. K HOMO MIXER, product made from Special machine Industry). Next, purified water was made to distribute for 1 minute as 100 ml, and the barium sulfate contrast medium for CT was prepared. (C-1)

In the comparative example 2 comparative example 1, 1.5 g was used for barium sulfate (it is below the same). (C-2)

In the comparative example 3 comparative example 1, 2.5 g was used for barium sulfate (it is below the same). (C-3)

In the comparative example 4 comparative example 1, 3.5 g was used for barium sulfate (it is below the same). (C-4)

In the comparative example 5 comparative example 1, 4.5 g was used for barium sulfate (it is below the same). (C-5) Let the sample Y be C series above.

B. Each five samples which carried out test-method production were created, and it put into the container made from a 300-ml plastic, and was neglected in the cool place for 30 days. 30 days afterward, each sample was made to shake for 40 seconds with a shaker (THERMONICS, THERMO-SHAK-ER MODEL Z-1 type), and the concentration of barium sulfate was analyzed with the weight method (how to extract 20 ml of samples and to calculate the barium sulfate content by an ashing method with a weight method). The result to the comparative example 1-5 was shown even with Example 1-5 in Table 1 about the average value and standard deviation of each analytical value.

表 1. 硫酸バリウム含量の平均値とその定量バラツキ

試 料	平均値	標準偏差	試 料	平均値	標準偏差
A-1	0.49	0.03	C-1	0.40	0.3
A-2	1.48	0.04	C-2	1.15	0.6
A-3	2.48	0.02	C-3	2.05	0.6
A-4	3.45	0.05	C-4	2.98	0.5
A-5	4.48	0.04	C-5	3.58	0.8
B-6	0.49	0.04			
B-7	1.49	0.04			
B-8	2.48	0.03			
B-9	3.44	0.06			
B-10	4.48	0.04			

As shown in table 1., the contrast medium concerning this invention is excellent in the redispersibility after prolonged neglect, and understands that the fixed-quantity standard deviation is also small compared with a comparative example. In Drawing 1, based on Table 1, barium sulfate concentration is shown on a horizontal axis, and a CT valve is shown on a vertical axis. A solid line is a thing of A series, it was shown that barium sulfate concentration and a CT valve have a straight-line relation, and standard deviation was shown up and down in each concentration. A dotted line is a thing of C series which is a comparative example, and since distribution is bad, it turns out that a CT valve range [ like the figure centering on 1.15% ] even 1.5% of whose thing like the comparative example C-2 is is shown. That is, it turns out that the expected CT valve is not obtained. If it is seen with the film on clinical [ actual ], it will see in Drawing 2 (example 2 sample A-2) and Drawing 3 (comparative example 2 sample C-2). Although contrast required of a diagnostic image when Drawing 2 has the good redispersibility of the 1.5% concentration of the sample A-2 is acquired, and Drawing 3 is similarly a diagnostic image at the time of the 1.5% concentration of the sample C-2, contrast required since redispersibility is bad is not acquired. When such contrast differs on a film, it cannot be overemphasized that it is inconvenient in diagnosis. For example, although the thing of 3% of concentration should show the CT valve of 470 (HU) essentially, it means that the CT valve of 250-400 (HU) is shown. On a film, this serves as a contrast difference, appears and causes

diagnosis top trouble.

[Effect of the Invention]As explained to details above, the barium sulfate contrast medium for CT concerning this explanation has good redispersibility by shaking by hand simply at the time of administration to a patient, and this invention shows the outstanding characteristic effect, namely, the additive of swelling nature like insoluble disintegrator in barium sulfate suspension — (— if it settles after there being physiological admission nature, and mixing insoluble in water nature high molecular compound) and agitating uniformly at the time of manufacture, barium sulfate and this additive free settling or flocking settling. It carries out, and mixes and sediments to the low side of a container, or on this additive, barium sulfate serves as a layer and will form a precipitated layer, i.e., a soft cake. That is, since barium sulfate does not touch an immediate container and it is easy to separate by re-shake by a hand from a container, and since the cake formed again is soft, it is thought that it is easy to be destroyed by little power that re dispersion is easy.

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## DESCRIPTION OF DRAWINGS

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[Brief Description of the Drawings]

Drawing 1 is a graph which shows a relation with the variation in the barium sulfate content shown in barium sulfate concentration, a CT valve, and Table 1. Drawing 2 is a diagnostic image of the sample A-2, and Drawing 3 is a diagnostic image of the sample C-2.

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